DOCKET NO.: ISIS-5031 Application No.: 10/087,424 Office Action Dated: June 3, 2004

This listing of claims will replace all prior versions, and listings, of claims in the application.

## **Listing of Claims:**

- 1-30 (Canceled)
- 31. (Currently amended) A method for preparing a library of compounds of the formula

wherein:

each tether moiety T is  $=\frac{NH(R^{\dagger})NH-}{-NHR^{\dagger}NH-}$ ,  $-NH(R^{\dagger})O-$ ,  $-NHR^{2}NH-$ ,  $-NHR^{2}SO_{2}NH-$ ,  $-NHR^{1}-$ ,  $-N(R^{4})_{2}$ , -N=N-, O, S, Se,  $-P(=O)(O)_{2}$ , NH, OR<sup>2</sup>, OR<sup>3</sup>, malonato, pyrrolidinyl, piperidinyl, piperazinyl, morpholino, imidazolyl, pyrrolyl, pyrazolyl, indolyl, 1H-indolyl,  $\alpha-$ carbolinyl, carbazolyl, phenothiazinyl, phenoxazinyl, tetrazolyl, or triazolyl;

 $R^1$  is alkylene;  $R^2$  is aryl;  $R^3$  is H or  $C_1$ - $C_{10}$  alkyl;  $R^4$  is alkyleneoxy; and

each chemical substituent L is, independently,  $C_1$ - $C_{10}$  alkyl, substituted  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl, substituted  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{10}$  alkynyl, substituted  $C_2$ - $C_{10}$  alkynyl,  $C_4$ - $C_7$  carbocyclic

**Application No.: 10/087,424** 

Office Action Dated: June 3, 2004

alkyl, substituted C<sub>4</sub>-C<sub>7</sub> carbocyclic alkyl, C<sub>4</sub>-C<sub>10</sub> alkenyl carbocyclic, substituted C<sub>4</sub>-C<sub>10</sub> alkenyl carbocyclic, C<sub>4</sub>-C<sub>10</sub> alkynyl carbocyclic, substituted C<sub>4</sub>-C<sub>10</sub> alkynyl carbocyclic, C<sub>6</sub>-C<sub>14</sub> aryl, substituted C<sub>6</sub>-C<sub>14</sub> aryl, heteroaryl, substituted heteroaryl, a nitrogen, oxygen or sulfur containing heterocycle, a substituted nitrogen, oxygen or sulfur containing heterocycle, a mixed heterocycle, or a substituted mixed heterocycle; wherein each of the substituent groups is selected from a group consisting of alkyl, alkenyl, alkynyl, aryl, hydroxyl, alkoxy, benzyl, nitro, thiol, thioalkyl, thioalkoxy and halo; or L is, independently, phthalimido, an ether having 2 to 10 carbon atoms and 1 to 4 oxygen or sulfur atoms, hydrogen, halogen, hydroxyl, thiol, keto, carboxyl, NR1R2, CONR1, amidine, guanidine, glutamyl, nitro, nitrate, nitrile, trifluoromethyl, trifluoromethoxy, NH-alkyl, N-dialkyl, O-aralkyl, S-aralkyl, NH-aralkyl, azido, hydrazino, hydroxylamino, sulfoxide, sulfone, sulfide,

contacting a purine heterocyclic scaffold having at least two functionalizable atoms, wherein at least one of said functionalizable atoms is blocked, with a mixture of at least six different chemical substituents to append each of said chemical substituents to said heterocyclic scaffold directly to form a substituent-appended scaffold;

disulfide, silyl, a nucleosidic base, an amino acid side chain, or a carbohydrate, comprising:

deblocking at least one of said blocked functionalizable atom atoms of said substituent-appended scaffold; and

contacting said substituent-appended scaffold with a mixture of at least six different chemical substituents to append each of said chemical substituents to said substituent-appended scaffold either directly or via a tether moiety covalently attached to one of said functionalizable atoms.

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**DOCKET NO.: ISIS-5031** 

Application No.: 10/087,424

Office Action Dated: June 3, 2004

32. (Previously presented) The method of claim 31 wherein said compounds of said

library are within 20 mole percent of equimolarity.

33. (Previously presented) The method of claim 31 wherein said contacting steps are

carried out in one reaction vessel.

34. (Canceled)

35. (Previously presented) The method of claim 31 wherein said scaffold is contacted

with a mixture of at least ten different chemical substituents.

36. (Previously presented) The method of claim 31 wherein said scaffold is contacted

with a mixture of at least fifteen different chemical substituents.

37. (Previously presented) The method of claim 31 wherein said method is performed

in solution phase.

38. (Currently amended) A method for preparing a library of compounds of the formula:

Page 4 of 11

DOCKET NO.: ISIS-5031 Application No.: 10/087,424 Office Action Dated: June 3, 2004

wherein:

each tether moiety T is  $= NH(R^{\dagger})NH - NHR^{1}NH - NH(R^{1})O - NHR^{2}NH - NHR^{2}SO_{2}NH - NHR^{1} - N(R^{4})_{2}$ , -N=N-, O, S, Se,  $-P(=O)(O)_{2}$ , NH, OR<sup>2</sup>, OR<sup>3</sup>, malonato, pyrrolidinyl, piperidinyl, piperazinyl, morpholino, imidazolyl, pyrrolyl, pyrazolyl, indolyl, 1H-indolyl,  $\alpha$ -carbolinyl, carbazolyl, phenothiazinyl, phenoxazinyl, tetrazolyl, or triazolyl;

 $R^1$  is alkylene;  $R^2$  is aryl;  $R^3$  is H or  $C_1$ - $C_{10}$  alkyl;  $R^4$  is alkyleneoxy; and

each chemical substituent L is, independently,  $C_1$ - $C_{10}$  alkyl, substituted  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl, substituted  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{10}$  alkynyl, substituted  $C_2$ - $C_{10}$  alkynyl,  $C_4$ - $C_7$  carbocyclic alkyl,  $C_4$ - $C_{10}$  alkenyl carbocyclic, substituted  $C_4$ - $C_{10}$  alkenyl carbocyclic, substituted  $C_4$ - $C_{10}$  alkynyl carbocyclic,  $C_6$ - $C_{14}$  aryl, substituted  $C_6$ - $C_{14}$  aryl, heteroaryl, substituted heteroaryl, a nitrogen, oxygen or sulfur containing heterocycle, a substituted nitrogen, oxygen or sulfur containing heterocycle, a mixed heterocycle,

**DOCKET NO.: ISIS-5031** 

**Application No.: 10/087,424** 

Office Action Dated: June 3, 2004

or a substituted mixed heterocycle; wherein each of the substituent groups is selected from a group

consisting of alkyl, alkenyl, alkynyl, aryl, hydroxyl, alkoxy, benzyl, nitro, thiol, thioalkyl, thioalkoxy

and halo; or L is, independently, phthalimido, an ether having 2 to 10 carbon atoms and 1 to 4

oxygen or sulfur atoms, hydrogen, halogen, hydroxyl, thiol, keto, carboxyl, NR1R2, CONR1, amidine,

guanidine, glutamyl, nitro, nitrate, nitrile, trifluoromethyl, trifluoromethoxy, NH-alkyl, N-dialkyl,

O-aralkyl, S-aralkyl, NH-aralkyl, azido, hydrazino, hydroxylamino, sulfoxide, sulfone, sulfide,

disulfide, silvl, a nucleosidic base, an amino acid side chain, or a carbohydrate, comprising:

contacting a purine heterocyclic scaffold having at least two functionalizable atoms, wherein

at least one of said functionalizable atoms is blocked, with a mixture of at least six different chemical

substituents to append each of said chemical substituents to said heterocyclic scaffold via a tether

moiety covalently attached to one of said functionalizable atoms to form a substituent-appended

scaffold;

deblocking at least one of said blocked functionalizable atom atoms of said

substituent-appended scaffold; and

contacting said substituent-appended scaffold with a mixture of at least six different chemical

substituents to append each of said chemical substituents to said substituent-appended scaffold either

directly or via a tether moiety covalently attached to one of said functionalizable atoms.

39. (Previously presented) The method of claim 38 wherein said compounds of said

library are within 20 mole percent of equimolarity.

Page 6 of 11

DOCKET NO.: ISIS-5031 Application No.: 10/087,424

Office Action Dated: June 3, 2004

40. (Previously presented) The method of claim 38 wherein said contacting steps are carried out in one reaction vessel.

## 41. (Canceled)

- 42. (Previously presented) The method of claim 38 wherein said scaffold is contacted with a mixture of at least ten different chemical substituents.
- 43. (Previously presented) The method of claim 38 wherein said scaffold is contacted with a mixture of at least fifteen different chemical substituents.
- 44. (Previously presented) The method of claim 38 wherein said method is performed in solution phase.
  - 45. (Currently amended) A method for preparing a library of compounds of the formula:

DOCKET NO.: ISIS-5031 Application No.: 10/087,424 Office Action Dated: June 3, 2004

wherein:

each tether moiety T is =NH(R<sup>†</sup>)NH- -NHR<sup>1</sup>NH-, -NH(R<sup>1</sup>)O-, -NHR<sup>2</sup>NH-, -NHR<sup>2</sup>SO<sub>2</sub>NH-, -NHR<sup>1</sup>-, -N(R<sup>4</sup>)<sub>2</sub>, -N=N-, O, S, Se, -P(=O)(O)<sub>2</sub>, NH, OR<sup>2</sup>, OR<sup>3</sup>, malonato, pyrrolidinyl, piperidinyl, piperazinyl, morpholino, imidazolyl, pyrrolyl, pyrazolyl, indolyl, 1H-indolyl,  $\alpha$ -carbolinyl, carbazolyl, phenothiazinyl, phenoxazinyl, tetrazolyl, or triazolyl;

 $R^1$  is alkylene;  $R^2$  is aryl;  $R^3$  is H or  $C_1$ - $C_{10}$  alkyl;  $R^4$  is alkyleneoxy; and

each chemical substituent L is, independently,  $C_1$ - $C_{10}$  alkyl, substituted  $C_1$ - $C_{10}$  alkyl,  $C_2$ - $C_{10}$  alkenyl, substituted  $C_2$ - $C_{10}$  alkenyl,  $C_2$ - $C_{10}$  alkynyl, substituted  $C_2$ - $C_{10}$  alkynyl,  $C_4$ - $C_7$  carbocyclic alkyl,  $C_4$ - $C_{10}$  alkenyl carbocyclic, substituted  $C_4$ - $C_{10}$  alkenyl carbocyclic,  $C_4$ - $C_{10}$  alkynyl carbocyclic, substituted  $C_4$ - $C_{10}$  alkynyl carbocyclic,  $C_6$ - $C_{14}$  aryl, substituted  $C_6$ - $C_{14}$  aryl, heteroaryl, substituted heteroaryl, a nitrogen, oxygen or sulfur containing heterocycle, a substituted nitrogen, oxygen or sulfur containing heterocycle, a mixed heterocycle,

**DOCKET NO.: ISIS-5031** 

Application No.: 10/087,424

Office Action Dated: June 3, 2004

or a substituted mixed heterocycle; wherein each of the substituent groups is selected from a group consisting of alkyl, alkenyl, alkynyl, aryl, hydroxyl, alkoxy, benzyl, nitro, thiol, thioalkyl, thioalkoxy and halo; or L is, independently, phthalimido, an ether having 2 to 10 carbon atoms and 1 to 4 oxygen or sulfur atoms, hydrogen, halogen, hydroxyl, thiol, keto, carboxyl, NR¹R², CONR¹, amidine,

guanidine, glutamyl, nitro, nitrate, nitrile, trifluoromethyl, trifluoromethoxy, NH-alkyl, N-dialkyl,

O-aralkyl, S-aralkyl, NH-aralkyl, azido, hydrazino, hydroxylamino, sulfoxide, sulfone, sulfide,

disulfide, silyl, a nucleosidic base, an amino acid side chain, or a carbohydrate, comprising:

contacting a purine heterocyclic scaffold molecule having a plurality of functionalizable atoms with

a mixture of at least six different chemical substituents in one reaction vessel to append each of said

chemical substituents to said scaffold either directly or via a tether moiety covalently attached to one

of said functionalizable atoms.

46. (Previously presented) The method of claim 45 wherein said compounds of said library are within 20 mole percent of equimolarity.

47. (Canceled)

(Previously presented) The method of claim 45 wherein said scaffold is contacted 48.

with a mixture of at least ten different chemical substituents.

Page 9 of 11

DOCKET NO.: ISIS-5031 Application No.: 10/087,424

Office Action Dated: June 3, 2004

49. (Previously presented) The method of claim 45 wherein said scaffold is contacted with a mixture of at least fifteen different chemical substituents.

50. (Previously presented) The method of claim 45 wherein said method is performed in solution phase.